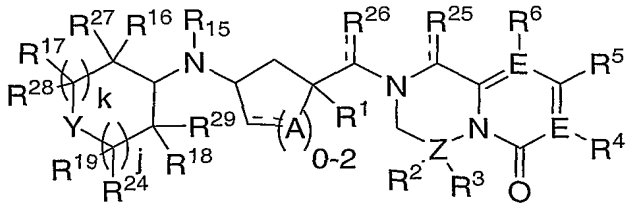
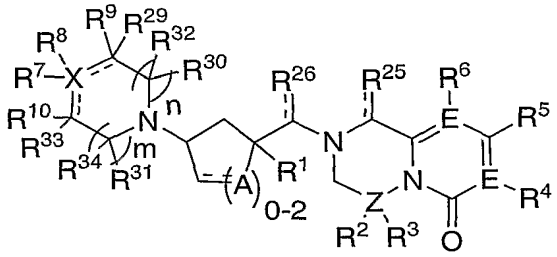
WHAT IS CLAIMED IS:

1. A compound of Formula I or Formula II:



I



II

wherein:

A is selected from: $-CH_2-$, -O-, $-N(R^{20})-$, -S-, -SO-, $-SO_2-$, $-N(SO_2R^{14})-$, and $-N(COR^{13})-$;

E is independently selected from N and C;

X is O, N, S, SO_2 or C;

Y is selected from: -O-, $-N(R^{20})-$, -S-, -SO-, $-SO_2-$, and $-C(R^{21})(R^{22})-$, $-N(SO_2R^{14})-$, $-N(COR^{13})-$, $-C(R^{21})(COR^{11})-$, $-C(R^{21})(OCOR^{14})-$ and -CO-;

Z is selected from C, N or O;

R^1 is selected from: hydrogen, $-C_{1-6}$alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -SO-C_{1-6}alkyl, $-SO_2-C_{1-6}$alkyl, $-SO_2NR^{12}R^{12}$, $-NR^{12}-SO_2-NR^{12}R^{12}$, $-(C_{0-6}alkyl)-(C_{3-7}cycloalkyl)-(C_{0-6}alkyl)$, -CN, $-NR^{12}R^{12}$, $-NR^{12}COR^{13}$, $-NR^{12}SO_2R^{14}$, $-COR^{11}$, $-CONR^{12}R^{12}$, $-NR^{12}CONR^{12}R^{12}$, -O-CO-C_{1-6}alkyl, -O-CO_2-C_{1-6}alkyl, hydroxy, heterocycle and phenyl,

where said alkyl and cycloalkyl are unsubstituted or substituted with 1-7 substituents independently selected from: halo, hydroxy, -O-C_{1-6}alkyl unsubstituted or substituted with 1-6 fluoro, C_{1-6}alkyl unsubstituted or substituted with 1-6 fluoro, -$CONR^{12}R^{12}$, -$NR^{12}CONR^{12}R^{12}$, -COR^{11}, -SO_2R^{14}, -$NR^{12}COR^{13}$, -$NR^{12}SO_2R^{14}$, -heterocycle, =O, -CN, phenyl, -$SO_2NR^{12}R^{12}$, -NR^{12}-SO_2-$NR^{12}R^{12}$, -S-C_{1-6}alkyl unsubstituted or substituted with 1-6 fluoro, -SO-C_{1-6}alkyl unsubstituted or substituted with 1-6 fluoro, -SO_2-C_{1-6}alkyl, unsubstituted or substituted with 1-6 fluoro, and -O-COR^{13},

where said phenyl and heterocycle are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, -COR^{11}, C_{1-3}alkyl, and C_{1-3}alkoxy, said C_{1-3}alkyl and C_{1-3}alkoxy being unsubstituted or substituted with 1-6 fluoro;

R^2 and R^3 are nothing when Z is O;

R^2 is nothing and R^3 is hydrogen or C_{1-3}alkyl when Z is N;

R^2 and R^3 are independently hydrogen or C_{1-3}alkyl unsubstituted or substituted with 1-3 fluoro, when Z is C;

R^4 is selected from: hydrogen, C_{1-3}alkyl unsubstituted or substituted with 1-3 fluoro, -O-C_{1-3}alkyl unsubstituted or substituted with 1-3 fluoro, hydroxy, chloro, fluoro, bromo, phenyl and heterocycle, when E is C;

R^5 is selected from: fluoro, chloro, bromo, -heterocycle, -CN, -COR^{11}, C_{4-6}cycloalkyl, -O-C_{4-6}cycloalkyl, C_{1-6}alkyl unsubstituted or substituted with 1-6 fluoro or hydroxyl or both, -O-C_{1-6}alkyl unsubstituted or substituted with 1-6 fluoro, -CO-C_{1-6}alkyl unsubstituted or substituted with 1-6 fluoro, -S-C_{1-6}alkyl unsubstituted or substituted with 1-6 fluoro, -pyridyl unsubstituted or substituted with one or more substituents selected from halo, trifluoromethyl, C_{1-4}alkyl and COR^{11}, - phenyl unsubstituted or substituted with one or more substituents selected from halo, trifluoromethyl, C_{1-4}alkyl and COR^{11}, -O-phenyl unsubstituted or substituted with one or more substituents selected from halo, trifluoromethyl, C_{1-}

$_4$alkyl and COR^{11}, -C_{3-6}cycloalkyl unsubstituted or substituted with 1-6 fluoro, and -O-C_{3-6}cycloalkyl unsubstituted or substituted with 1-6 fluoro, when E is C;

R^6 is selected from: hydrogen, hydroxy, chloro, fluoro, bromo, phenyl, heterocycle, C_{1-3}alkyl unsubstituted or substituted with 1-3 fluoro and -O-C_{1-3}alkyl unsubstituted or substituted with 1-3 fluoro, when E is C;

$R^4$and R^6 are independantly selected from nothing or O (to make an N-oxide) when E is N;

R^7 is selected from: hydrogen, (C_{0-6}alkyl)-phenyl, (C_{0-6}alkyl)-heterocycle, (C_{0-6}alkyl)-C_{3-7}cycloalkyl , (C_{0-6}alkyl)-COR^{11}, (C_{0-6}alkyl)-(alkene)-COR^{11}, (C_{0-6}alkyl)-SO_3H, (C_{0-6}alkyl)-W-C_{0-4}alkyl, (C_{0-6}alkyl)-$CONR^{12}$-phenyl and (C_{0-6}alkyl)-$CONR^{23}$-V-COR^{11}, when X is N or C,

where W is selected from: a single bond, -O-, -S-, -SO-, -SO_2-, -CO-, -CO_2-, -$CONR^{12}$- and –NR^{12}-,

where V is selected from C_{1-6}alkyl or phenyl,

where R^{23} is hydrogen or C_{1-4}alkyl, or R^{23} is a 1-5 carbon linker to one of the carbons of V to form a ring,

where said C_{0-6}alkyl is unsubstituted or substituted with 1-5 substituents independently selected from: halo, hydroxy, -C_{0-6}alkyl, -O-C_{1-3}alkyl, trifluoromethyl and -C_{0-2}alkyl-phenyl,

where said phenyl, heterocycle, cycloalkyl and C_{0-4}alkyl, if present, are unsubstituted or substituted with 1-5 substituents independently selected from: halo, trifluoromethyl, hydroxy, C_{1-3}alkyl, -O-C_{1-3}alkyl, -C_{0-3}-COR^{11}, -CN, -$NR^{12}R^{12}$, -$CONR^{12}R^{12}$ and -C_{0-3}-heterocycle,

or where said phenyl or heterocycle is fused to another heterocycle, said other heterocycle being unsubstituted or substituted with 1-2 substituents independently selected from hydroxy, halo, -COR^{11}, and –C_{1-3}alkyl,

and where alkene is unsubstituted or substituted with 1-3 substituents which are independently selected from: halo, trifluoromethyl, C_{1-3}alkyl, phenyl and heterocycle;

R^7 is absent when X is O, S, or SO_2;

R^8 is selected from: hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyl-hydroxy, -O-C_{1-3}alkyl, -COR^{11}, -$CONR^{12}R^{12}$ and –CN, when X is C;

R^8 is nothing, when X is O, S, SO_2 or N, or when a double bond joins the carbons to which R^7 and R^{10} are attached;

or, R^7 and R^8 are joined to form a ring selected from: 1H-indene, 2,3-dihydro-1H-indene, 2,3-dihydro-benzofuran, 1,3-dihydro-isobenzofuran, 2,3-dihydro-benzothiofuran, 1,3-dihydro-isobenzothiofuran, 6*H*-cyclopenta[*d*]isoxazol-3-ol, cyclopentane and cyclohexane,

where said ring is unsubstituted or substituted with 1-5 substituents independently selected from: halo, trifluoromethyl, hydroxy, C_{1-3}alkyl, -O-C_{1-3}alkyl, -C_{0-3}-COR^{11}, -CN, -$NR^{12}R^{12}$, -$CONR^{12}R^{12}$ and -C_{0-3}alkyl-heterocycle;

R^9 and R^{10} are independently selected from: hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyl-COR^{11}, C_{1-6}alkyl-hydroxy, -O-C_{1-3}alkyl, halo;

or R^9 and R^{10} together are O, where O is connected to the ring via a double bond;

or, R^7 and R^9, or R^8 and R^{10}, are joined to form a fused ring which is phenyl or heterocycle, wherein said fused ring is unsubstituted or substituted with 1-7 substituents independently selected from: halo, trifluoromethyl, hydroxy, C_{1-3}alkyl, -O-C_{1-3}alkyl, -COR^{11}, -CN, -$NR^{12}R^{12}$ and -$CONR^{12}R^{12}$;

R^{11} is independently selected from: hydroxy, hydrogen, C_{1-6} alkyl, -O-C_{1-6}alkyl, benzyl, phenyl, C_{3-6} cycloalkyl , where said alkyl, phenyl, benzyl and cycloalkyl groups are unsubstituted or substituted with

1-6 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, -CO_2H, -CO_2-C_{1-6} alkyl, and trifluoromethyl;

R^{12} is selected from: hydrogen, C_{1-6} alkyl, benzyl, phenyl and C_{3-6} cycloalkyl, where said alkyl, phenyl, benzyl and cycloalkyl groups are unsubstituted or substituted with 1-6 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, -CO_2H, -CO_2-C_{1-6} alkyl, and trifluoromethyl;

or, when two separate R^{12} groups reside on the same atom or adjacent atoms, said two R^{12} groups are optionally connected via a C_{1-7}alkyl linker to form a 3 to 9 membered ring, said linker being unsubstituted or substituted with with 1-6 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, -CO_2H, -CO_2-C_{1-6} alkyl and trifluoromethyl;

R^{13} is selected from: hydrogen, C_{1-6} alkyl, -O-C_{1-6}alkyl, benzyl, phenyl and C_{3-6} cycloalkyl, where said alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-6 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, -CO_2H, -CO_2-C_{1-6} alkyl and trifluoromethyl;

R^{14} is selected from: hydroxy, C_{1-6} alkyl, -O-C_{1-6}alkyl, benzyl, phenyl and C_{3-6} cycloalkyl, where said alkyl, phenyl, benzyl and cycloalkyl groups are unsubstituted or substituted with 1-6 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, -CO_2H, -CO_2-C_{1-6} alkyl and trifluoromethyl;

R^{15} is hydrogen or C_{1-6}alkyl, where said alkyl is unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, -CO_2H, -CO_2C_{1-6}alkyl, and –O-C_{1-3}alkyl;

R^{16} is selected from: hydrogen, fluoro, C_{3-6} cycloalkyl, -O-C_{3-6}cycloalkyl, hydroxy, -COR^{11}, -$OCOR^{14}$, C_{1-6}alkyl unsubstituted or substituted with 1-6 substituents selected from fluoro, C_{1-3}alkoxy, hydroxyl and -COR^{11}, and -O-C_{1-3}alkyl unsubstituted or substituted with 1-3 fluoro;

or, R^{15} and R^{16} together are a C_{2-4}alkyl or a C_{0-2}alkyl-O-C_{1-3}alkyl, forming a ring where said ring has 5-7members;

R^{17} is selected from: hydrogen, COR^{11}, hydroxy,-O-C_{1-6}alkyl unsubstituted or substituted with 1-6 substituents selected from fluoro, C_{1-3}alkoxy, hydroxy, and -COR^{11} and C_{1-6}alkyl unsubstituted or substituted with 1-6 substituents selected from fluoro, C_{1-3}alkoxy, hydroxy, and -COR^{11}, or R^{17} is nothing if R^{28} is connected to a ring carbon via a double bond;

or, R^{16} and R^{17} together are C_{1-4}alkyl or C_{0-3}alkyl-O-C_{0-3}alkyl, forming ring where said ring has 3-7 members;

R^{18} is selected from: hydrogen, fluoro, -O-C_{3-6}cycloalkyl, -O-C_{1-3}alkyl unsubstituted or substituted with 1-6 fluoro and C_{1-6}alkyl unsubstituted or substituted with 1-6 fluoro;

or, R^{16} and R^{18} together areC_{2-3}alkyl, where said alkyl is unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, -COR^{11}, C_{1-3}alkyl, and C_{1-3}alkoxy;

or, R^{16} and R^{18} together areC_{1-2}alkyl-O-C_{1-2}alkyl, where said alkyl is unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, -COR^{11}, C_{1-3}alkyl, and C_{1-3}alkoxy;

or, R^{16} and R^{18} together are –O-C_{1-2}alkyl-O-, where said alkyl is unsubstituted or substituted with 1-3 substituents independently selected from halo, hydroxy, -COR^{11}, C_{1-3}alkyl, and C_{1-3}alkoxy;

R^{19} is selected from: hydrogen, COR^{11}, SO_2R^{14}, $SO_2NR^{12}R^{12}$ and C_{1-3}alkyl unsubstituted or substituted with 1-6 substituents independently selected from fluoro and hydroxyl;

R^{20} is selected from: hydrogen, C_{1-6} alkyl, benzyl, phenyl and C_{3-6} cycloalkyl, where said alkyl, phenyl, benzyl and cycloalkyl groups are unsubstituted or substituted with 1-6 substituents independently selected from halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, -CO_2H, -CO_2-C_{1-6} alkyl, and trifluoromethyl;

R^{21} and R^{22} are independently selected from: hydrogen, hydroxy, C_{1-6} alkyl, -O-C_{1-6}alkyl, benzyl, phenyl and C_{3-6} cycloalkyl where said alkyl, phenyl, benzyl, and cycloalkyl groups can be unsubstituted or substituted with 1-6 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, -CO_2H, -CO_2-C_{1-6} alkyl and trifluoromethyl;

R^{24} is selected from: hydrogen, COR^{11}, SO_2R^{14}, $SO_2NR^{12}R^{12}$ and C_{1-3}alkyl, where said alkyl is unsubstituted or substituted with 1-6 substituents independently selected from: fluoro and hydroxyl;

or, R^{24} and R^{17} together are a C_{1-3}alkyl bridge;

R^{25} and R^{26} are independently selected from: =O where R^{25} and/or R^{26} is oxygen and is connected via a double bond, hydrogen, phenyl, and C_{1-6}alkyl substituted or unsubstituted with 1-6 substituents selected from -COR^{11}, hydroxy, fluoro, chloro and C_{1-3}alkyl;

R^{27} is selected from: hydrogen, COR^{11}, SO_2R^{14}, $SO_2NR^{12}R^{12}$ and C_{1-3}alkyl, where said alkyl is unsubstituted or substituted with 1-6 substituents independently selected from fluoro and hydroxyl;

R^{28} is selected from selected from: hydrogen, hydroxy, halo, C_{1-3}alkyl unsubstituted or substituted with 1-6 substituents independently selected from fluoro and hydroxy, -$NR^{12}R^{12}$, -COR^{11}, -$CONR^{12}R^{12}$, -$NR^{12}COR^{13}$, -$OCONR^{12}R^{12}$, -$NR^{12}CONR^{12}R^{12}$, -heterocycle, -CN, -NR^{12}-SO_2-$NR^{12}R^{12}$, -NR^{12}-SO_2-R^{14}, -SO_2-$NR^{12}R^{12}$ and =O where R^{28} is connected to the ring via a double bond and where R^{17} at the same position is absent;

R^{29} and R^{33} are selected from: hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyl-COR^{11}, C_{1-6}alkyl-hydroxy, -O-C_{1-3}alkyl, trifluoromethyl and halo, or R^{29} or R^{33} are independently absent if the site of substitution is unsaturated;

or, R^{29} and R^{16} together are a C_{1-3}alkyl bridge;

R^{30} and R^{31} are independently selected from: hydroxy, C_{1-6}alkyl, C_{1-6}alkyl-COR^{11}, C_{1-6}alkyl-hydroxy, -O-C_{1-3}alkyl, halo and hydrogen, where said alkyl are unsubstituted or substituted with 1-6 substituents independantly selected from fluoro and hydroxyl;

or, R^{30} and R^{31} together are a -C_{1-4}alkyl-, -C_{0-2}alkyl-O-C_{1-3}alkyl- or –C_{1-3}alkyl-O-C_{0-2}alkyl-, where said alkyl are unsubstituted or substituted with 1-2 substituents consisting of oxy where the oxygen is joined to the bridge via a double bond, fluoro, hydroxy, methoxy, methyl or trifluoromethyl;

R^{32} and R^{34} are independently selected from: hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyl-COR^{11}, C_{1-6}alkyl-hydroxy, -O-C_{1-3}alkyl, trifluoromethyl and halo;

j is 0, 1, or 2;

k is 0, 1, or 2;

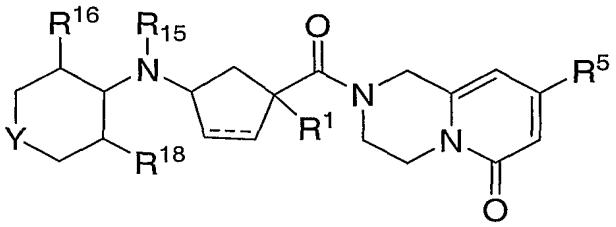
m is 0, 1, or 2;

n is 1 or 2;

the dashed line represents an optional single bond;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

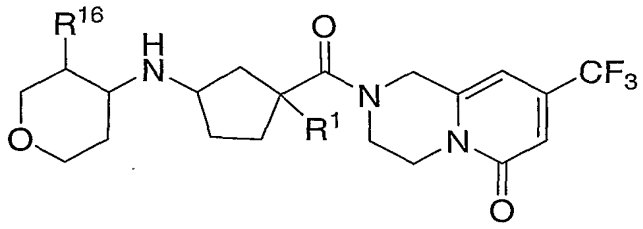
2. The compound of claim 1 of the Formula Ia:



Ia

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

3. The compound of claim 1 of the Formula Ib:



Ib

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

4. The compound of claim 1, wherein: A is CH_2, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

5. The compound of claim 1, wherein Y is O or CH_2, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

6. The compound of claim 1, wherein E is C, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

7. The compound of claim 1, wherein Z is C, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

8. The compound of claim 1, wherein R^1 is selected from: -C_{1-6}alkyl, -C_{0-6}alkyl-O-C_{1-6}alkyl, heterocycle, and -(C_{0-6}alkyl)-(C_{3-7}cycloalkyl)-(C_{0-6}alkyl), where said alkyl, heterocycle and cycloalkyl are unsubstituted or substituted with 1-7 substituents independently selected from halo, hydroxy, -O-C_{1-3}alkyl, trifluoromethyl, C_{1-3}alkyl, -O-C_{1-3}alkyl, -COR^{11}, -CN, -$NR^{12}R^{12}$, -$CONR^{12}R^{12}$ and -$NCOR^{13}$, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

9. The compound of claim 1, wherein R^1 is selected from: C_{1-6}alkyl, C_{1-6}alkyl substituted with hydroxy, and C_{1-6}alkyl substituted with 1-6 fluoro, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

10. The compound of claim 1, wherein R^1 is selected from: $-CH(CH_3)_2$, $-C(OH)(CH_3)_2$, $-CH(OH)CH_3$ and $-CH_2CF_3$, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

11. The compound of claim 1, wherein one or more of R^2, R^3 and R^4 is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

12. The compound of claim 1, wherein R^5 is selected from: C_{1-6}alkyl substituted with 1-6 fluoro, -O-C_{1-6}alkyl substituted with 1-6 fluoro, chloro, bromo and phenyl, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

13. The compound of claim 12, wherein R^5 is trifluoromethyl, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

14. The compound of claim 1, wherein R^{15} is methyl or hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

15. The compound of claim 1, wherein R^{16} is selected from: hydrogen, C_{1-3}alkyl which is unsubstituted or substituted with 1-6 fluoro, -O-C_{1-3}alkyl, fluoro and hydroxy, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

16. The compound of claim 1, wherein R^{16} is selected from: hydrogen, trifluoromethyl, methyl, methoxy, ethoxy, ethyl, fluoro and hydroxy, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

17. The compound of claim 1, wherein R^{17} is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

18. The compound of claim 1, wherein R^{18} is selected from: hydrogen, methyl, and methoxy, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

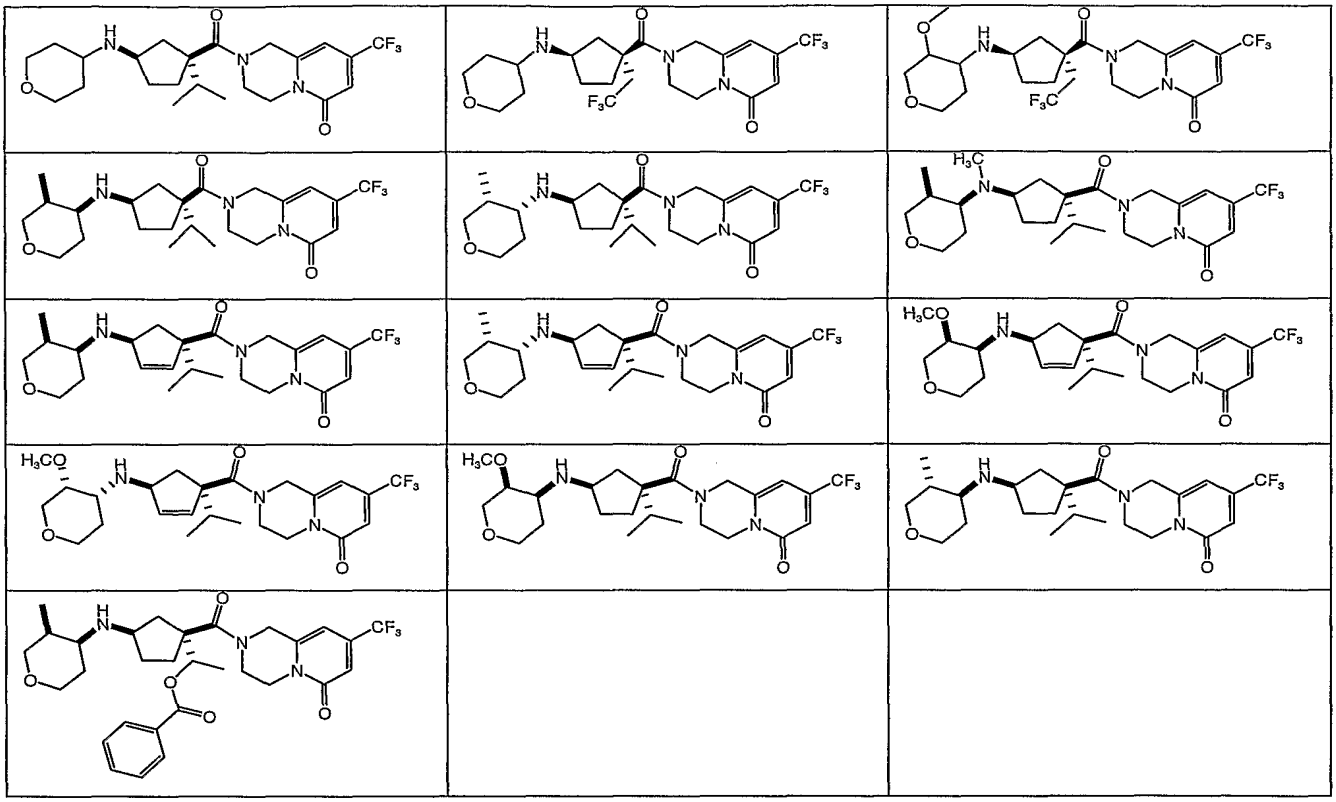
19. The compound of claim 1, R^{16} and R^{18} together are $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

20. The compound of claim 1, wherein one or more of R^{19}, R^{24} and R^{25} is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

21. The compound of claim 1, wherein R^{26} is O, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

22. The compound of claim 1, wherein one or more of R^{27}, R^{28} and R^{29} is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

23. A compound selected from:



and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

24. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

25. A method for modulations of chemokine receptor activity in a mammal which comprises the administration of an effective amount of a compound of Claim 1.

26. A method for treating, ameliorating, controlling or reducing the risk of an inflammatory and immunoregulatory disorder or disease which comprises the administration to a patient of an effective amount of a compound of Claim 1.

27. A method for treating, ameliorating, controlling or reducing the risk of rheumatoid arthritis which comprises the administration to a patient of an effective amount of a compound of Claim 1.